VALUE IN HEALTH 18 (2015) 783–790

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

Cost-Effectiveness of Mirabegron Compared with Antimuscarinic Agents for the Treatment of Adults with Overactive Bladder in the United Kingdom

Jameel Nazir, MSc[1,], Khaled Maman, MSc[2], Mohamed-Elmoctar Neine, MSc[3], Benjamin Briquet, MSc[3], Isaac A.O. Odeyemi, DVM, PhD[1], Zalmai Hakimi, PharmD[4], Andy Garnham, MSc[1], Samuel Aballéa, MSc[3]*

[1]*Astellas Pharma Europe Ltd, Chertsey, Surrey, UK;* [2]*Creativ-Ceutical Ltd., London, UK;* [3]*Creativ-Ceutical SARL, Saint Honoré, Paris, France;* [4]*Astellas Pharma Global Development, Leiden, The Netherlands*

ABSTRACT

Background: Mirabegron, a first-in-class selective oral β_3-adrenoceptor agonist, has similar efficacy to most antimuscarinic agents and a lower incidence of dry mouth in patients with overactive bladder (OAB). **Objectives:** To evaluate the cost-effectiveness of mirabegron 50 mg compared with oral antimuscarinic agents in adults with OAB from a UK National Health Service perspective. **Methods:** A Markov model including health states for symptom severity, treatment status, and adverse events was developed. Cycle length was 1 month, and the time horizon was 5 years. Antimuscarinic comparators were tolterodine extended release, solifenacin, fesoterodine, oxybutynin extended release and immediate release (IR), darifenacin, and trospium chloride modified release. Transition probabilities for symptom severity levels and adverse events were estimated from a mirabegron trial and a mixed treatment comparison. Estimates for other inputs were obtained from published literature or expert opinion. Quality-adjusted life-years (QALYs) and total health care costs, including costs of drug acquisition, physician visits, incontinence pad use, and botox injections, were modeled. Deterministic and probabilistic sensitivity analyses were performed. **Results:** Base-case incremental cost-effectiveness ratios ranged from £367 (vs. solifenacin 10 mg) to £15,593 (vs. oxybutynin IR 10 mg) per QALY gained. Probabilistic sensitivity analyses showed that at a willingness-to-pay threshold of £20,000/QALY gained, the probability of mirabegron 50 mg being cost-effective ranged from 70.2% versus oxybutynin IR 10 mg to 97.8% versus darifenacin 15 mg. A limitation of our analysis is the uncertainty due to the lack of direct comparisons of mirabegron with other agents; a mixed treatment comparison using rigorous methodology provided the data for the analysis, but the studies involved showed heterogeneity. **Conclusions:** Mirabegron 50 mg appears to be cost-effective compared with standard oral antimuscarinic agents for the treatment of adults with OAB from a UK National Health Service perspective.

Keywords: antimuscarinic drugs, cost-effectiveness analysis, mirabegron, overactive bladder.

Introduction

Overactive bladder (OAB) is characterized by urinary urgency, usually accompanied by frequency and nocturia, with or without urgency urinary incontinence [1]. The UK National Institute for Health and Clinical Excellence (NICE) recommends bladder training and lifestyle advice as first-line treatments for OAB, followed by primary pharmacotherapy with antimuscarinic agents or mirabegron (Betmiga; Astellas) [2,3]. Antimuscarinic agents are not selective because they inhibit muscarinic receptors in tissues such as salivary glands and brain, as well as those in the bladder, the therapeutic target in patients with OAB. This lack of specificity results in adverse events (AEs) such as dry mouth, blurred vision, and constipation [4], which adversely affect treatment adherence and persistence [5]; dry mouth is a common cause of treatment withdrawal [6]. In contrast, mirabegron, a first-in-class selective oral β_3-adrenoceptor agonist that enhances urine storage through stimulation of bladder β_3-adrenoceptors, has similar efficacy to antimuscarinic therapy, but improved tolerability, with an incidence of dry mouth similar to that with placebo [7–10].

We developed a Markov model to analyze the cost-effectiveness of mirabegron compared with oral antimuscarinic agents for the treatment of adults with OAB from a UK National Health Service (NHS) perspective.

Methods

Model Overview

We developed a Markov model to simulate the therapeutic management of OAB, including AEs of treatment, and to predict costs and

Presented in part at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) 16th Annual European Congress, November 2–6, 2013, Dublin, Ireland.

* *Address correspondence to:* Jameel Nazir, Astellas Pharma Europe Ltd., 2000 Hillswood Drive, Chertsey, Surrey KT16 0RS, UK.
E-mail: Jameel.Nazir@astellas.com.

1098-3015$36.00 – see front matter © 2015 Published by Elsevier Inc. on behalf of International Society for Pharmacoeconomics and Outcomes Research (ISPOR).
http://dx.doi.org/10.1016/j.jval.2015.05.011

quality-adjusted life-years (QALYs) gained after treatment with mirabegron 50 mg or antimuscarinic therapy. Data from a mixed treatment comparison (MTC) were used to estimate differences in mean changes from baseline in daily numbers of micturition and incontinence episodes and odds ratios of AEs between mirabegron and antimuscarinic agents [11]. Estimates for other probabilities, resources, and costs were obtained from the literature. Additional input regarding parameters with limited data was obtained from six clinical experts.

The cycle length of the model was 1 month, and the time horizon was 5 years; real-world data show that 65% to 86.5% of the patients discontinue therapy within 1 year [12]. The model was programmed in Microsoft Excel 2007.

MTC

A Bayesian MTC based on a systematic literature search was used to estimate the relative efficacy and safety of mirabegron compared with placebo and the following antimuscarinic agents: tolterodine extended release (ER) 4 mg and immediate release (IR) 4 mg; darifenacin 7.5 or 15 mg; solifenacin 5 or 10 mg; fesoterodine 4 or 8 mg; oxybutynin ER 10 mg and IR 10 or 15 mg; and trospium chloride modified release 60 mg [11].

Health States

The following elements were used to define the health states that were considered:

1. *OAB severity* based on daily numbers of micturition and incontinence episodes. These symptoms of OAB were found to have a significant influence on utility independently of each other, with moderate correlations between changes in these symptoms (unpublished data captured in 2012). The progression of each of these symptoms over time was therefore modeled separately. Each symptom had five severity levels, which were assigned a different utility decrement, and was considered independently.
2. *Treatment status for OAB*.
3. *Presence or absence of AEs*, specifically dry mouth and constipation, which had a direct effect on utilities and were associated with an increased probability of treatment switch or discontinuation.

These events are associated with antimuscarinic agents [4]; the events reported most frequently with mirabegron occur at a similar incidence as with placebo [9].

A model transition diagram is shown in Figure 1. At model entry, patients were distributed across 25 symptom severity profiles and were assigned to treatment with either mirabegron or an antimuscarinic agent. Each month, the symptom severity profile was reassessed according to changes in the frequency of micturition and incontinence. Probabilities of symptomatic changes were dependent on treatment status.

Treatment Pathway

At model entry, patients were assigned to treatment with oral mirabegron 50 mg once daily or an antimuscarinic agent (Fig. 2). Every month, patients could switch to the next line of OAB treatment in case of treatment failure or AEs. In case of failure of the next line of therapy, a small proportion of patients received botulinum toxin (BTX); this was based on UK clinical practice as validated by a panel of experts (unpublished data captured in 2012). The model did not allow for treatment with an antimuscarinic agent after failure of BTX.

Model Input Parameters

Baseline symptom severity

The initial distribution of patients by symptom severity level was obtained from the phase 3 SCORPIO trial of mirabegron, based on pooled data from all treatment arms at baseline (see Appendix Table 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.05.011). SCORPIO is the name used for trial 178-CL-046, registered as NCT00689104. The official title is: A Randomized, Double-Blind, Parallel Group, Placebo and Active Controlled, Multicenter Study to Assess the Efficacy and Safety of Mirabegron in Subjects With Symptoms of Overactive Bladder.

Transition probabilities between symptom severity levels

Transition probabilities between symptom severity levels were derived from multinomial logistic equations. We initially estimated a multinomial logistic model by regression analysis on data from the SCORPIO trial [9]. Because there were five levels of severity, the model included four coefficients capturing the effect of treatment on the probabilities of moving to different severity levels. Other covariates included in the model were sex, age, and current severity level. A calibration method was then used [13] to fit this model to mean changes in symptoms at 3 months, determined from the MTC for different products. The parameters

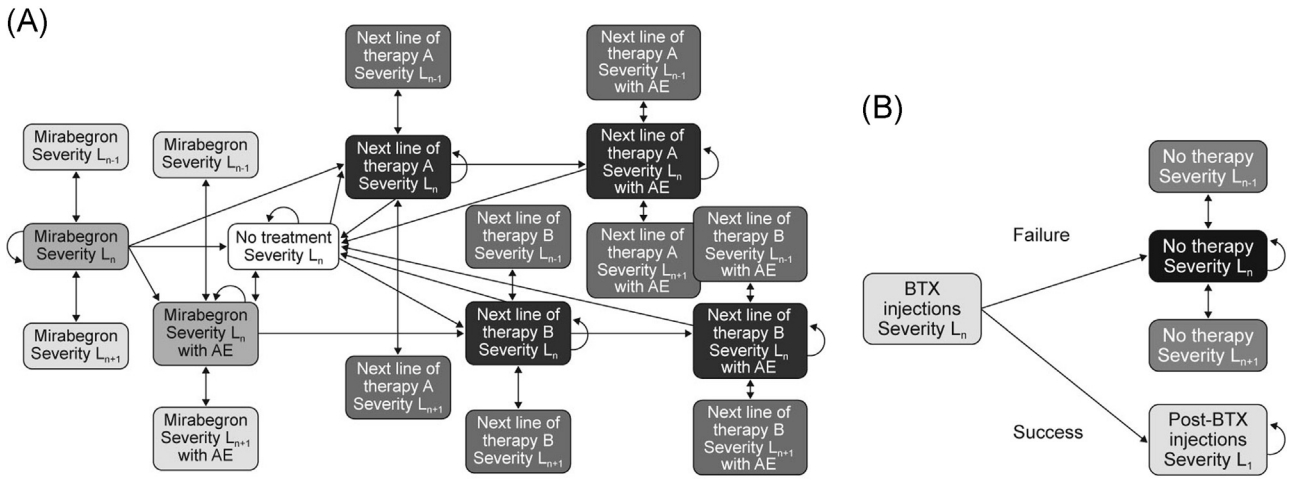

Fig. 1 – Model transition diagram: (A) before initiation of BTX and (B) after initiation of BTX. AE, adverse event; BTX, botulinum toxin; Severity L, symptom severity level.

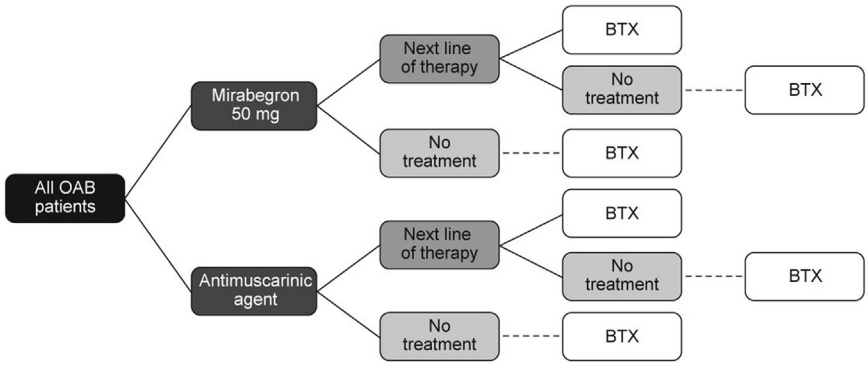

Fig. 2 – Treatment pathway. BTX, botulinum toxin; OAB, overactive bladder.

varied in the calibration were the four treatment coefficients from the logistic regression equation and the calibration targets were the mean changes in symptoms at 3 months. Thus, the four treatment coefficients in the logistic model for a given treatment were obtained by modifying the coefficients initially estimated for mirabegron to minimize the distance between the mean change in symptoms at 3 months from baseline predicted by the economic model and the mean change determined from the MTC (see Appendix Table 1). The resulting equations were used to generate the transition matrices for each product and symptom (see Appendix Table 2 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.05.011).

After 3 months, probabilities were assumed to be constant, consistent with evidence from a long-term study suggesting that the treatment effect of antimuscarinic therapy at 4 months is maintained to 24 months [14]. For patients discontinuing treatment, the proportions by symptom severity level were assumed to be the same as at baseline.

Treatment discontinuation

In this model, the discontinuation rate was disaggregated so that patients discontinued because of either AEs (dry mouth or constipation) or other reasons (lack of efficacy or other reasons) (Table 1). Because no discontinuation rates were available specifically for AEs, it was assumed that 90% of the patients experiencing AEs would discontinue treatment; a lower value (50%) was used in the sensitivity analysis to test the impact of this assumption. For patients who discontinued because of other causes, data were taken from Wagg et al. [12], who reported real-world discontinuation rates for antimuscarinic agents including solifenacin, darifenacin, tolterodine ER, tolterodine IR, oxybutynin ER, and oxybutynin IR. These rates were used because discontinuation rates in clinical trials are generally lower than those in clinical practice. Castro-Diaz et al. [15] reported that 24% of the patients discontinue treatment because of AEs. These data were used to calculate monthly treatment-specific probabilities of discontinuation for reasons other than AEs for the base-case model (Table 1). Because there were no real-life persistence data for mirabegron, the conservative assumption that the persistence rate for mirabegron was equal to that for the comparator in the absence of AEs was made. For the sensitivity analysis, the mean duration of treatment was estimated to be 156.7 days (5.2 months) [12], which corresponds to a monthly discontinuation rate of 14.5%, assuming that the discontinuation hazard is constant over time.

Treatment switch

The probability of treatment switch for the base-case analysis (26.06%) was taken from a study of treatment patterns among patients with OAB in the United Kingdom (Table 1) [16]. Among 5424 patients who received tolterodine as first-line therapy, 68.92% discontinued treatment within the study period and 26.06% of these switched to another medication. For the sensitivity analysis, an analysis of US health insurance claims data showed that 13.3% of all patients switched to another medication over a period of 12 months and 13.2% of the patients were persistent at 12 months [17]. This suggests that 15.32% of the patients discontinuing an antimuscarinic agent switch to another medication.

BTX

The probability of symptomatic improvement after BTX injection was taken from the literature (Table 1) [18]. No data about the probability of switching to BTX or receiving BTX following a period without treatment were identified in the literature. We assumed that 1% of the patients on next-line therapy or having discontinued next-line therapy switched to BTX every year.

AEs

As described, two AEs, dry mouth and constipation, were considered and used to define specific health states. Data were derived from the SCORPIO trial [9] or the MTC (Table 1) [11].

Utilities

Utility values according to symptom severity were derived from the EuroQol five-dimensional questionnaire (EQ-5D) index scores from all treatment arms of the SCORPIO trial (Astellas, data on file), using previously reported methodology [19]. A linear regression model was used to estimate EQ-5D index scores as a function of symptom severity level (Table 1), as well as age, sex, and country. The utility values used for the base-case model are presented in Appendix Table 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.05.011. Utilities derived from the Overactive Bladder Questionnaire, using the algorithm developed by Yang et al. [20], were used for the sensitivity analysis (see Appendix Table 3). A disutility for AEs was also estimated on the basis of a repeated regression analysis of the SCORPIO EQ-5D data (Table 1). This was applied for the duration of a cycle for patients who experienced AEs and stayed on treatment.

Resource utilization and costs

Inputs for resources and costs are presented in Table 2. Costs were evaluated from a UK NHS payer perspective and presented in 2012 GBP (£). The following direct medical costs and resources were considered in the model:

1. *Drug acquisition costs:* Patients were assumed to use 1 tablet per day until discontinuation. Drug wastage and partial compliance were not considered.

Table 1 – Model inputs for efficacy, adverse events, and utilities.

Parameter	Base-case value	Sensitivity analysis values	Source
Efficacy			
Monthly probability of BTX injection	0.01%	0%–0.05%	Assumption
Probability of success with BTX	79%	50%–100%	[18]
Monthly probability of treatment discontinuation			
Without adverse events			[12,15]; assumption
Tolterodine	6.4%	3%–14.5%	
Solifenacin	5.5%		
Fesoterodine	6.4%		
Oxybutynin	7.3%		
Trospium chloride	6.7%		
Darifenacin	7.9%		
With adverse events	90%	50%–100%	Assumption
Monthly probability of treatment switch*	26.06%	15.32%–50%	[16,17]; assumption
Monthly probability of treatment restart†	5.6%	0%–10%	Assumption
Adverse events‡			
Dry mouth			
Mirabegron 50 mg	2.8%	2.1%–3.5%	[9]
Tolterodine ER 4 mg	10.9%	8.7%–11.5%	[11]
Solifenacin 5 mg	10.8%	6.5%–16.6%	[11]
Solifenacin 10 mg	22.9%	14.8%–32.4%	[11]
Fesoterodine 4 mg	11.6%	7.2%–17.5%	[11]
Fesoterodine 8 mg	22.3%	15.0%–30.8%	[11]
Oxybutynin IR 10 mg	29.6%	8.7%–11.5%	[11]
Oxybutynin ER 10 mg	16.9%	8.7%–11.5%	[11]
Trospium chloride 60 mg	12.3%	10.1%–25.6%	[11]
Darifenacin 7.5 mg	13.0%	4.6%–25.0%	[11]
Darifenacin 15 mg	19.4%	6.6%–22.1%	[11]
Constipation			
Mirabegron 50 mg	1.6%	1%–2.2%	[9]
Tolterodine ER 4 mg	1.8%	1.41%–2.6%	[11]
Solifenacin 5 mg	3.7%	2.2%–6.0%	[11]
Solifenacin 10 mg	6.4%	3.9%–10.0%	[11]
Fesoterodine 4 mg	1.7%	0.9%–2.8%	[11]
Fesoterodine 8 mg	3.0%	1.8%–4.7%	[11]
Oxybutynin IR 10 mg	1.6%	1.0%–2.2%	[11]
Oxybutynin ER 10 mg	1.6%	0.8%–2.8%	[11]
Trospium chloride 60 mg	11.0%	3.3%–26.9%	[11]
Darifenacin 7.5 mg	2.7%	1.3%–5.0%	[11]
Darifenacin 15 mg	4.9%	2.6%–8.2%	[11]
Utilities according to symptom severity derived from EQ-5D index scores§			
Micturition			
Level 1	0.0632	0.0453–0.0811	
Level 2	0.0422	0.0258–0.0587	
Level 3	0.0204	0.0045–0.0363	
Level 4	0.0104	–0.0054 to 0.0262	
Incontinence			
Level 1	0.0586	0.0422–0.0749	
Level 2	0.0437	0.0271–0.0602	
Level 3	0.0314	0.0142–0.0486	
Level 4	0.0128	–0.0056 to 0.0313	
Decrement for adverse events	–0.0357	–0.1 to 0	

BTX, botulinum toxin; EQ-5D, EuroQol five-dimensional questionnaire; ER, extended release; IR, immediate release.

* Among patients discontinuing medication for overactive bladder.

† Because no data were found in the literature regarding the probability of restarting treatment, we assumed a monthly probability of 5.6% (50% annually) for restarting treatment among patients who discontinued treatment without immediately switching to another drug. It was assumed that one-third of these patients would go back to their previous treatment, one-third would receive "next line A," and the remainder would receive "next line B."

‡ Three-month probabilities.

§ Coefficients for symptom severity level relative to symptom level 5; e.g., the utility of patients at micturition severity level 1 is higher than the utility of patients with micturition severity level 5 by 0.0632.

Table 2 – Model inputs for resource use and costs.

Parameter	Base-case value	Sensitivity analysis values	Source
Resource use			
Pad utilization, no. per day*			Astellas, data on file
Level 1	0.17	0.150–0.198	
Level 2	0.75	0.687–0.817	
Level 3	1.38	1.282–1.486	
Level 4	1.89	1.745–2.039	
Level 5	3.34	3.167–3.511	
GP consultations	1 visit at start and each switch	0–2	[21]; expert opinion
Specialist consultations	1.5 visits at start and each switch	1–3	[21]; expert opinion
BTX reinjections†	0.17/mo	0–0.34	Expert opinion
Costs (£)			
Monthly acquisition cost			
Mirabegron 50 mg	29.40	–	[22]
Tolterodine ER 4 mg	28.01	–	[22]
Solifenacin 5 mg	28.00	–	[22]
Solifenacin 10 mg	36.41	–	[22]
Fesoterodine 4 mg	28.01	–	[22]
Fesoterodine 8 mg	28.01		[22]
Oxybutynin IR 10 mg	3.24	–	[22]
Oxybutynin ER 10 mg	27.92	–	[22]
Trospium chloride 60 mg	25.04	–	[22]
Darifenacin 7.5 mg	27.68		[22]
Darifenacin 15 mg	27.68		[22]
GP consultation	36	–	[23]
Specialist visit	96	–	[24]
BTX injection/reinjection	1158/964	–	[25]
Incontinence pad	0.16	–	[26]

BTX, botulinum toxin; ER, extended release; IR, immediate release; GP, general practitioner.
* According to incontinence symptom severity level.
† Following successful first injection.

2. *Primary care visits:* General practitioner visits were assumed to occur only on initiation of a new medication [21].
3. *Specialist visits:* 1.5 outpatient urologist visits on the initiation of a new medication were assumed [21].
4. *BTX injections:* The cost of BTX injections included acquisition and administration costs. If treatment was successful, it was assumed that injections were repeated at 6-month intervals.
5. *Incontinence pads:* The mean number of pads used per day in the SCORPIO trial (all treatment groups) was calculated by incontinence severity level.

Discount Rate

A discount rate of 3.5% per year was applied to costs and health benefits.

Model Assumptions

Assumptions applied in the model are presented in Appendix Table 4 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.05.011.

Model Outputs

The primary cost-effectiveness measure was the incremental cost-effective ratio (ICER), expressed as cost per QALY gained. A willingness-to-pay threshold of £20,000/QALY gained was used to interpret ICERs.

Sensitivity Analyses

The impact of uncertainty surrounding parameter estimates was assessed. ICERs were recalculated using 95% confidence intervals around each parameter or other fixed values in a deterministic sensitivity analysis [11]. Input variables with uncertainties were varied simultaneously according to predefined distributions (data not shown) in a probabilistic sensitivity analysis.

Results

Base-Case Scenario

The model predicts that the maximum proportion of patients remaining on mirabegron treatment after 5 years was 6.2% (Table 3). The cost-effectiveness findings for the base-case scenario are presented in Table 4 (see also Appendix Tables 5–14 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.05.011). ICERs ranged from £367 to £15,593/QALY gained compared with solifenacin 10 mg and oxybutynin IR 10 mg, respectively. All were below the willingness-to-pay threshold of £20,000/QALY gained.

Deterministic Sensitivity Analyses

The deterministic sensitivity analyses showed that ICERs are generally most sensitive to transition probabilities between severity levels, the baseline distribution of patients across severity levels, and the probabilities of treatment discontinuation and dry mouth (for solifenacin 5 mg) (see Appendix Fig. 1 in

Table 3 – Proportion of patients remaining on their initial treatment (5-y time frame).

Treatment	Comparator (%)	Mirabegron 50 mg (%)
Tolterodine ER 4 mg	2.8	4.9
Solifenacin 5 mg	2.9	6.2
Solifenacin 10 mg	1.4	6.2
Fesoterodine 4 mg	2.7	4.9
Fesoterodine 8 mg	1.3	3.4
Oxybutinin ER 10 mg	2	4.6
Oxybutinin IR 10 mg	1.2	3.9
Trospium chloride 60 mg	1.6	4.5
Darifenacin 7.5 mg	1.9	3.4
Darifenacin 15 mg	1.8	6.2

ER, extended release; IR immediate release.

Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.05.011).

Probabilistic Sensitivity Analyses

Probabilistic sensitivity analyses showed that the probability of mirabegron 50 mg being cost-effective compared with tolterodine ER 4 mg was 92.6%, darifenacin 7.5 and 15 mg 97.7% and 97.8%, respectively, solifenacin 5 and 10 mg 86.6% and 92.8%, respectively, fesoterodine 4 and 8 mg 93.4% and 97.1%, respectively, oxybutynin ER 10 mg and IR 10 mg 95.9% and 70.2%, respectively, and trospium chloride 60 mg 78.2% (see Appendix Figs. 2 and 3 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2015.05.011).

Discussion

This analysis shows that from a UK NHS perspective, mirabegron is cost-effective compared with oral antimuscarinic agents commonly used for the treatment of adults with OAB. This is a result of improved persistence and patients' quality of life on mirabegron due to the lower risk of AEs. All ICERs were below the willingness-to-pay threshold of £20,000/QALY gained [27]. Deterministic sensitivity analyses showed that the model is sensitive to transition probabilities between symptom levels and probabilities of discontinuation, but the probability of ICERs being less than £20,000 was high. These findings complement and support existing efficacy and safety data for mirabegron [7–10].

Several other Markov models for the treatment of OAB, all based on a structure developed by Kobelt et al. [28], have been reported. This model consisted of five health states representing different levels of disease severity with a time horizon of 1 year. Key limitations of the model relate to uncertainty and subsequent changes in treatment pathways, with patients now receiving more therapies because of the increase in treatment options. We developed a Markov model that considered the main OAB symptoms of micturition frequency and incontinence, as well as health states for treatment discontinuation with and without AEs, and captured costs and outcomes after treatment discontinuation. Other strengths of our model include the quality of the SCORPIO trial data [9], the use of a time horizon of 5 years, and inclusion of utilities based on both generic (EQ-5D) and disease-specific (Overactive Bladder Questionnaire) instruments. The final model was validated and verified according to recognized guidelines [29,30].

Table 4 – Cost-effectiveness analysis of mirabegron 50 mg compared with other antimuscarinics at 5 y (base-case scenario).

Parameter	Tolterodine ER 4 mg	Solifenacin 5 mg	Solifenacin 10 mg	Fesoterodine 4 mg	Fesoterodine 8 mg	Oxybutynin IR 10 mg	Oxybutynin ER 10 mg	Trospium chloride 60 mg	Darifenacin 7.5 mg	Darifenacin 15 mg
Difference in the cost (£) of										
Drugs of interest	112.99	150.95	177.49	118.63	153.54	386.23	151.03	204.72	109.03	227.22
Other OAB drug(s)	−30.37	−42.16	−75.72	−32.25	−45.21	−58.50	−43.05	−52.15	−29.16	−66.61
GP visits	−4.71	−6.58	−11.62	−4.99	−6.81	−8.82	−6.60	−7.95	−4.43	−10.27
Specialist visits	−18.82	−26.34	−46.47	−19.97	−27.23	−35.27	−26.39	−31.80	−17.72	−41.08
BTX	−9.67	−13.23	−24.72	−10.29	−15.35	−19.84	−14.04	−17.22	−9.69	−21.51
Pads	−11.42	−5.00	−15.13	−12.38	−18.24	−19.24	−17.07	−11.32	−22.23	−21.24
Incremental costs (£)	38.00	57.65	3.83	38.74	40.69	244.56	43.87	84.28	25.79	66.52
Incremental QALYs	0.0104	0.0045	0.0105	0.0107	0.0123	0.0157	0.0135	0.0097	0.0132	0.0172
ICER, cost per QALY gained (£)	3,668.20	12,856.57	366.59	3,632.82	3,315.42	15,593.27	3,245.68	8,647.29	1,953.79	3,887.14

BTX, botulinum toxin; ER, extended release; GP, general practitioner; ICER, incremental cost-effectiveness ratio; IR, immediate release; OAB, overactive bladder; QALY, quality-adjusted life-year.

An important limitation of the analysis was the uncertainty around efficacy data for antimuscarinic agents, because no direct comparisons of mirabegron with these agents exist. The data used were therefore based on an MTC of randomized controlled trials [11]. Although rigorous methodology was used, the results should be considered with caution given the heterogeneity of the studies involved. Furthermore, because the MTC provided estimates of mean changes in micturitions and incontinence episodes for each treatment, transition probabilities between symptom levels were obtained using a calibration method. However, results for mirabegron versus tolterodine are similar whether based on probabilities directly estimated from the SCORPIO trial [31] or using the MTC and calibration.

Further limitations related to the use of assumptions or expert opinion when limited or no published data were available for certain parameters, for example, use of BTX and specialist visits. Also, because of lack of real-world data for mirabegron at the time that the analysis was performed, we assumed that the rate of mirabegron discontinuation for reasons other than AEs was equal to that of the comparator agent (the rate varied according to the comparison made). This is reasonable given that the efficacy of mirabegron and antimuscarinic therapy is similar [7,9], and the sensitivity analyses showed that discontinuation rates had little impact. However, it should be noted that subsequently reported real-world data indicate that persistence rates for mirabegron are better than those for antimuscarinic agents [32–34]. Furthermore, the model considered only two AEs, dry mouth and constipation, on the basis of a report showing that these events are most likely to cause treatment switch [6] and are therefore the main drivers of AE-related discontinuation. However, the events reported most frequently with mirabegron occur at a similar incidence with placebo [9].

The analysis reported here was submitted to the UK NICE as part of the Single Technology Appraisal for mirabegron. NICE found that the mirabegron trials used were well designed and that data were consistent across the trials. It also found that the economic analysis was well constructed, transparent, and accurate and that the primary base case was robust with respect to parameter uncertainty. Furthermore, the calibration techniques used to incorporate the MTC data to improve the accuracy of estimates from the economic model were viewed positively. In contrast, the approach to implementing discontinuation into the economic model was considered a weakness because it hindered comparison of modeled results with real-world data and assumed a variable rate for mirabegron. However, as noted above, the approach taken was conservative and may have underestimated the benefit of mirabegron. As part of this appraisal, the Evidence Review Group (ERG) also conducted a meta-analysis of the direct evidence and an MTC for the indirect evidence. The results of ERG's MTC were mainly in agreement with those of the MTC used here, although the outcomes of some comparisons of micturition or incontinence episode frequency between mirabegron and specific antimuscarinic agents differed. However, sensitivity analyses carried out by the ERG found the base-case model used to be generally robust with respect to the areas of uncertainty identified by the ERG.

The current NICE guidelines stipulate the use of generic IR formulations of antimuscarinic agents first line (oxybutynin IR and tolterodine IR). The efficacy of IR and ER formulations is assumed to be similar, whereas the associated incidence of dry mouth, constipation, and blurred vision differs. In the MTC, data were pooled from studies using IR and ER formulations of various antimuscarinic agents to estimate efficacy and safety. The present study does not distinguish IR and ER formulations in terms of discontinuation rates, but given that IR formulations are associated with higher rates of dry mouth [12], one would expect decreased persistence with IR formulations and ICERs potentially in favor of mirabegron, depending on the cost of IR formulations. A price sensitivity analysis showed that mirabegron remains cost-effective at the current British National Formulary price even when the price of tolterodine is reduced by 30%.

In conclusion, treatment with mirabegron 50 mg appears to be a cost-effective strategy compared with oral antimuscarinic agents in adults with OAB from a UK NHS perspective.

Acknowledgment

Editorial support was provided by Andy Noble of Bioscript Medical.

Source of financial support: This study was sponsored by Astellas Pharma Global Development. Editorial support provided by Andy Noble of Bioscript Medical was also funded by Astellas Pharma Global Development.

Supplemental Material

Supplemental material accompanying this article can be found in the online version as a hyperlink at doi:10.1016/j.jval.2015.05.011 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

REFERENCES

[1] Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010;29:4–20.
[2] National Institute for Health and Clinical Excellence. CG97 Lower Urinary Tract Symptoms: NICE Guideline. London, UK: 2010.
[3] National Institute for Health and Clinical Excellence. CG171 Urinary Incontinence in Women: NICE Guideline. Royal College of Obstetricians and Gynaecologists. London, UK: 2013.
[4] MacDiarmid SA. Concomitant medications and possible side effects of antimuscarinic agents. Rev Urol 2008;10:92–8.
[5] Oefelein MG. Safety and tolerability profiles of anticholinergic agents used for the treatment of overactive bladder. Drug Saf 2011;34:733–54.
[6] Compion G, Jackson J, Janes J. Reasons for switching antimuscarinic therapy: results from a European cross-sectional survey of physicians, and patients with OAB. Presented at: 27th Annual Congress of the European Association of Urology. Paris, France, 2012. Poster 691.
[7] Chapple CR, Kaplan SA, Mitcheson D, et al. Randomized double-blind, active-controlled phase 3 study to assess 12-month safety and efficacy of mirabegron, a β(3)-adrenoceptor agonist, in overactive bladder. Eur Urol 2013;63:296–305.
[8] Herschorn S, Barkin J, Castro-Diaz D, et al. A phase III, randomized, double-blind, parallel-group, placebo-controlled, multicentre study to assess the efficacy and safety of the β_3 adrenoceptor agonist, mirabegron, in patients with symptoms of overactive bladder. Urology 2013;82:313–20.
[9] Khullar V, Amarenco G, Angulo JC, et al. Efficacy and tolerability of mirabegron, a β(3)-adrenoceptor agonist, in patients with overactive bladder: results from a randomised European-Australian phase 3 trial. Eur Urol 2013;63:283–95.
[10] Nitti VW, Auerbach S, Martin N, et al. Results of a randomized phase III trial of mirabegron in patients with overactive bladder. J Urol 2013;189:1388–95.
[11] Maman K, Aballea S, Nazir J, et al. Comparative efficacy and safety of medical treatments for the management of overactive bladder: a systematic literature review and mixed treatment comparison. Eur Urol 2013;65:755–65. Supplemental appendix available from: http://www.europeanurology.com/article/S0302-2838(13)01207-4/fulltext/comparative-efficacy-and-safety-of-medical-treatments-for-the-management-of-overactive-bladder-a-systematic-literature-review-and-mixed-treatment-comparison#section-appendix-a-supplementary-data.
[12] Wagg A, Compion G, Fahey A, Siddiqui E. Persistence with prescribed antimuscarinic therapy for overactive bladder: a UK experience. BJU Int 2012;110:1767–74.

[13] Vanni T, Karnon J, Madan J, et al. Calibrating models in economic evaluation: a seven-step approach. Pharmacoeconeconomics 2011;29:35–49.
[14] Van Kerrebroeck PE, Heesakkers J, Berriman S, et al. Long-term safety, tolerability and efficacy of fesoterodine treatment in subjects with overactive bladder symptoms. Int J Clin Pract 2010;64:584–93.
[15] Castro-Diaz D, Miranda P, Sanchez-Ballester F, et al. Assessment of reasons for overactive bladder treatment change [in Spanish]. Actas Urol Esp 2011;35:73–9.
[16] Odeyemi IA, Dakin HA, O'Donnell RA, et al. Epidemiology, prescribing patterns and resource use associated with overactive bladder in UK primary care. Int J Clin Pract 2006;60:949–58.
[17] D'Souza AO, Smith MJ, Miller LA, et al. Persistence, adherence, and switch rates among extended-release and immediate-release overactive bladder medications in a regional managed care plan. J Manag Care Pharm 2008;14:291–301.
[18] Wu JM, Siddiqui NY, Amundsen CL, et al. Cost-effectiveness of botulinum toxin A versus anticholinergic medications for idiopathic urge incontinence. J Urol 2009;181:2181–6.
[19] Desroziers K, Aballea S, Maman K, et al. Estimating EQ-5D and OAB-5D health state utilities for patients with overactive bladder. Health Qual Life Outcomes 2013;11:200.
[20] Yang Y, Brazier J, Tsuchiya A, Coyne K. Estimating a preference-based single index from the Overactive Bladder Questionnaire. Value Health 2009;12:159–66.
[21] Cardozo L, Thorpe A, Warner J, Sidhu M. The cost-effectiveness of solifenacin vs fesoterodine, oxybutynin immediate-release, propiverine, tolterodine extended-release and tolterodine immediate-release in the treatment of patients with overactive bladder in the UK National Health Service. BJU Int 2010;106:506–14.
[22] British National Formulary. London, UK: BMJ Group, RCPCH Publications Ltd and the Royal Pharmaceutical Society of Great Britain. Available from: http://www.bnf.org/bnf/index.htm. [Accessed September 1, 2012].
[23] Personal Social Services Research Unit. Unit costs of health and social care, 2010. Available from: http://www.pssru.ac.uk/pdf/uc/uc2010/uc2010_s10.pdf. [Accessed July 1, 2014].
[24] National Health Service UK. National Health Service payment by results, tariff information spreadsheet 2010-2011. Available from: http://data.gov.uk/dataset/payment-by-results-2010-11-national-tariff-information. [Accessed June 15, 2013].
[25] Nottingham Urology Group. Bladder botox injections. Available from: http://www.nottinghamurologygroup.co.uk/treatments/bladder-botox-injections. [Accessed July 1, 2014].
[26] Age UK. The latest incontinence products & incontinence advice. Available from: http://www.ageukincontinence.co.uk/. [Accessed July 1, 2014].
[27] Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors influence its decisions? A binary choice analysis. Health Econ 2004;13:437–52.
[28] Kobelt G, Jönsson L, Mattiasson A. Cost-effectiveness of new treatments for overactive bladder: the example of tolterodine, a new muscarinic agent: a Markov model. Neurourol Urodyn 1998;17:599–611.
[29] Philips Z, Ginnelly L, Sculpher M, et al. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technol Assess 2004;8:iii–v, ix–xi, 1–158.
[30] Weinstein MC, O'Brien B, Hornberger J, et al. Principles of good practice for decision analytic modeling in health-care evaluation: report of the ISPOR Task Force on Good Research Practices–Modeling Studies. Value Health 2003;6:9–17.
[31] Aballéa S, Maman K, Desroziers K, et al. Cost effectiveness of mirabegron compared with tolterodine extended release for the treatment of adults with overactive bladder in the United Kingdom. Clin Drug Investig 2015;35:83–93.
[32] Nitti VW, Rovner E, Franks B, et al. Early experience with mirabegron: comparative persistence of mirabegron and tolterodine extended release in patients with overactive bladder. Presented at: 14th AUGS/IUGA Scientific Meeting. Washington, DC, USA, July 22–26, 2014. Abstract 1957.
[33] Wagg A, Franks B, Ramos B, Berner T. Persistence and adherence with mirabegron, a new beta-3 receptor agonist, versus antimuscarinics in overactive bladder: early experience in Canada. Presented at: ISPOR 17th Annual European Congress. November 8–12, 2014. Amsterdam, Netherlands. Abstract PUK28.
[34] Ogihara K, Kaguyama H, Sakamoto H, et al. Persistence with mirabegron in patients with overactive bladder: a comparative study of mirabegron and antimuscarinics. Presented at: ICS October 20–24, 2014. Rio de Janeiro, Brazil. Abstract 576.